REMARKS

Rejection under 35 USC § 103

The present claims are rejected under 35 USC § 103 as being unpatentable over Brodehorst, Brinkley, Merrifield and Massey. The examiner asserts that it "would have been prima facie obvious to one skilled in the art at the time the invention to synthesize the peptide carrier molecule as disclosed by Bredehorst et al. on a solid-support as disclosed by Merrifield because Merrifield explicitly states that his solid phase synthesis technology is ideally suited for peptide synthesis, which would encompass the insulin peptide disclosed by Bredehorst et al." (Office Action, page 7).

The present invention is directed to a method for producing conjugates that are useful in immunological assays. Using the methods of the present invention, structurally well-defined conjugates can be reproducibly produced. In particular, the present methodology allows for the precise positioning of haptens, labels and immobilization groups. Prior to Applicant's invention, it was difficult to control the structures of such conjugates, as evidenced by the references cited by the examiner.

Claim 33 requires two steps: "(a) forming a linear carrier on a solid phase by linking amino acids; and (b) introducing into the carrier 1-10 additional amino acids covalently bound to hapten molecules and 1-10 additional amino acids covalently bound to luminescent metal chelates or biotin,wherein the hapten molecules, the luminescent metal chelates, and the biotin are bound to the carrier through a side group selected from the group consisting of amino groups, thiol groups, and a combination thereof."

Claim 34 requires four steps: "(a) **forming a linear carrier on a solid phase** by linking amino acids; (b) **introducing** into the carrier additional **amino acids comprising protected reactive side groups**; (c) deprotecting the reactive side groups; and (d) coupling 1-10 hapten molecules and 1-10 luminescent metal chelates or biotin groups to the reactive side groups..."

Merrifield is the only reference of record that describes solid phase synthesis. Brodehorst, Brinkley, nor Massey relate to solid phase synthesis.

Merrifield teaches a method of solid phase synthesis – but fails to teach how to form a conjugate – especially a conjugate where the hapten, metal chelates or biotin are attached to the polypeptide via the side chains of amino acids. The only peptide formed by Merrifield is the tetrapeptide L-leucyl-L-alanylglycyl-L-valine. None of the amino acids in this tetrapeptide have side chains which contain a reactive amine or thiol. Instead, the amino acids have side chains which are either alkyl (leucine, alanine, and valine) or hydrogen (glycine). Merrifield describes sequential addition of amino acid residues to a forming polypeptide tethered to a solid support. Key to Merrifield's synthesis is that the newly added amino acid is N-terminally protected and is resistant to deprotection during the coupling stage. Thereafter, the N-terminal protecting group is removed. In the cited Merrifield paper, the N-terminal protecting group is the carbobenzoxy group (Cbz), which is removable under highly acidic conditions with hydrogen bromide and glacial acetic acid (page 2150, col. 1, under "Cleavage of the Amino-Protecting Group").¹

There is no teaching in Merrifield that these conditions are suitable for use with amino acid building blocks with side chains containing protected thiol or amine groups (as in Claim 34). At most, Merrifield discloses that the N,N'-dicyclohexylcarbodiimide method (DCC method) can be used to couple the glycylvalyl polymer to a variety of Cbz-protected amino acid residues (page 2150, Section entitled "The Peptide-Forming Step"). However, Merrifield specifically states that the DCC method had not been studied with lysine (page 2151, col. 1, lines 4-5). Moreover, he fails to disclose coupling those reagents to each other (versus the solid support).

Bredehorst describes the solution phase synthesis of a trifunctional carrier molecule for the florescent labeling of haptens. Brinkley provides a "brief survey of methods for preparing protein conjugates with dyes, haptens, and cross-linking

¹ The examiner suggests that Merrifield discloses cleavage of a Cbz protecting group with base, i.e. NaOH, in Figure 1. Cbzo can not be cleaved with base. Merrifield explains on page 2151, col. 1, 2nd paragraph, that the final decarbobenzoxylation was accomplished with HBr and that the deprotected peptide was then freed from the solid support by saponification (i.e. NaOH) or be vigorous HBr treatment.

reagents." All of the modifications discussed by Brinkley are made to an already formed biopolymer. Massey relates to electrochemiluminescent assays.

Attached is the declaration of Dr. Milan Mrksich. The arguments set forth in that declaration are incorporated in their entirety into this response. In particular, Dr. Mrksich testifies:

19. In sum, the examiner has asserted one with ordinary skill in the art would have, at the time of the invention, recognized the combined teachings of the Bredehorst, Brinkley, Merrifield and Massey references. Notwithstanding my disagreement with several of the assertions made by the Examiner, I strongly disagree that one with ordinary skill in the art, at the time of the invention, would have been familiar with each of these references and would have recognized the combined teachings in the manner postulated by the Examiner. In hindsight, the Examiner's arguments can be interpreted in a manner that is consistent with the Office Action, but at the time of the invention, this argument calls for a level of insight and expertise that were very clearly beyond one of ordinary skill in the art.

In view of these arguments and the declaration, the examiner is requested to remove the pending rejection and allow this case.

Conclusion:

If for any reason the Examiner feels that the above Amendments and Remarks do not put the claims in condition to be allowed, and that a discussion would be helpful, it is respectfully requested that the Examiner contact the undersigned agent directly at (312)-321-4283.

Respectfully submitted,

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